ORIGINAL ARTICLE

# Acute hepatitis B in the era of immunisation: pitfalls in the identification of high risk patients

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**Background:** Since the adoption of a universal hepatitis B immunisation strategy, the reported incidence of acute hepatitis B has declined dramatically worldwide including in Israel. However, new cases of acute hepatitis B still occur. The aim of this study was to describe the incidence of acute hepatitis B in a referral area, routes of transmission, and outcome.
**Methods:** The charts of all new hepatitis B patients, who visited the clinic in the years 2002 and 2003 (January 2002 to December 2003), were reviewed. The main criteria for a diagnosis of acute hepatitis B were transient increase of alanine transaminase activity, and hepatitis B surface antigen seroconversion.
**Results:** Twenty nine men and seven women were diagnosed with acute hepatitis B infection during the study period. Two patients were previously vaccinated with hepatitis B vaccine. One case of hepatitis D coinfection was reported. The incidence of acute hepatitis B in the referral area was estimated as 2.25 per 100 000 adult population. Mean age was 36 years (17–75). Twenty one patients (18 men and 3 women) acquired the virus through unprotected sexual contact, and seven patients through iatrogenic exposure. Thirty three patients underwent spontaneous seroconversion while three patients became chronic carriers.
**Conclusions:** Despite a universal immunisation policy, frequent cases of acute hepatitis B in Israel are still seen. High risk heterosexual activity and iatrogenic exposure seem to be the commonest routes of transmission. Further recommendations regarding vaccination policy are discussed.

Since the introduction of a hepatitis B vaccination policy worldwide, a significant decline in acute hepatitis B virus (HBV) infection has been reported.[1] In 1992, the Global Advisory Group to the World Health Organisation recommended that all countries integrate the hepatitis B vaccine into national immunisation programmes by 1997. In the USA, routine infant vaccination was started in 1992, and later expanded (second half of the 1990s) to include adolescents, and specific high risk adults.[1 2] Various countries have interpreted the WHO recommendations differently.[3] In a study conducted by the Centers For Disease Control and Prevention (CDC), hepatitis B incidence was followed up in four countries for a period of 17 years. Overall, a 76.1% decline in acute hepatitis B cases was seen.[1] Furthermore, in the year 2000, 8036 cases of acute hepatitis B were reported in the USA, compared with 33 605 cases reported in 1987, with a calculated incidence of 2.87 per 100 000 population.[4]

The frequency of HBV infection and patterns of HBV transmission vary considerably in different parts of the world. In countries with a low HBV prevalence, ranging from 0.1% to 2%,[2] a shift in the mode of HBV acquisition was noted. In the past two decades, high risk heterosexual contact has become the leading route of viral transmission.[5 6] Other common routes of hepatitis B transmission are injection drug use, percutaneous inoculation, and blood born viral transfusion. Israel harbours an intermediate HBV prevalence, with 2%–7% hepatitis B surface antigen positive patients.[2] HBV vaccination policy in Israel followed that of the USA, and since 1992 all newborns have been vaccinated. Additional recommendations for HBV vaccination in the Israeli population are similar to those in the USA, with the exception of the high risk heterosexual population, who are included in USA but not the Israeli vaccination policy.

The aim of this study was to examine the incidence of acute HBV infection in a tertiary referral centre in Israel, and to describe the main routes of viral transmission, so as to estimate the efficacy of the current vaccination policy.

## METHODS

This retrospective study was conducted at a tertiary referral centre, the liver unit, part of the gastroenterology department in the Tel-Aviv Sourasky Medical Center (TASMC), Israel. This clinical study was performed in accordance with the ethical principles for medical research involving human subjects as stated in the declaration of Helsinki. The patients' information was obtained by reviewing all charts of newly diagnosed hepatitis B patients who presented to our clinic during the calendar years 2002 and 2003, between 1 January 2002 and 31 December 2003. Information collected included demographic characteristics, medical history, date of illness onset, history of travel, history of blood product transfusion, previous hospitalisation or medical procedures, sexual habits including number of partners in the past year, household medical status, and outcome of the illness. Patients reporting having more than one partner in a six month period were considered to display high risk sexual behaviour. Serology for hepatitis A, B, C, and D viruses and for HIV was evaluated at the time of first visit, and again six months later. Laboratory analysis performed included hepatitis A IgG and IgM antibodies, hepatitis B surface antigen (HBsAg), antihepatitis B surface antibody (anti-HBs Ab), hepatitis B core IgG and IgM antibodies, hepatitis B envelope antigen, antihepatitis B envelope antibody, HBV DNA (by PCR), and hepatitis D IgG and IgM antibodies. HIV was evaluated using the ELISA technique. A full biochemistry panel including alanine transaminase (ALT) and aspartate transaminase (AST) activities (upper normal limit values: ALT 39 U/l for men, 25 U/l for women, AST 40 U/l for men and women), complete blood count and coagulation tests (prothrombin time, partial thromboplastin time, international normalised ratio) were evaluated in the first and on each clinical visit. A diagnosis of

**Abbreviations:** HBV, hepatitis B virus; ALT, alanine transaminase; AST, aspartate transaminase; HBsAg, hepatitis B surface antigen; anti-HBs Ab, antihepatitis B surface antibody

acute HBV infection was based on patient's history suggestive of high risk exposure, and the fulfilment of both: (1) hepatitis B surface antigen seroconversion and/or presence of hepatitis B IgM core antibodies (2) transient increase of ALT to more than five times the upper normal limit.[1 2] Patients were examined monthly and chronic HBV status was determined after a period of six months from the first serological evidence of acute hepatitis B infection. During the study period all newly infected patients received supportive treatment only.

## RESULTS

### Demographics and clinical characteristics

During the years 2002–2003, 63 new patients referred to our unit had a positive serology test for hepatitis B (29 patients in 2002, 34 patients in 2003). Of the 63 patients, 36 (47.6%) were diagnosed with acute HBV infection. There were 29 men and seven women (table 1).

The mean age was 36 years (17–75 years). The mean maximal ALT was 52.2 times the upper normal limit (15–187 upper normal limit). In one case, the patient had coinfection with hepatitis A, while in another case hepatitis D coinfection was reported. All patients were tested negative for HIV. Three patients (8.33%) became chronic carriers as was evidenced by seroconversion from HBsAg negativity before infection to HBsAg positivity lasting longer than six months. Thirty three patients (91.66%) underwent spontaneous seroconversion. None of the patients developed fulminant liver failure, and none died.

### Disease incidence

We estimated an incidence of 2.25 cases of acute HBV infection per 100 000 adults at our referral centre based on our data from the years 2002–2003, with the population in Israel's coastal plain area estimated at 800 000 adults.

### Previous vaccination

Two patients were previously vaccinated with HBsAg vaccine (three injections during a six month period, each). One patient did not develop a protective antibody titre. Data regarding the second patient's immune status after vaccination (HBs antibodies) were not available.

### Risk factors for infection

Altogether 33 of 36 patients reported here as having acute hepatitis B infection had a recognised risk factor for acquiring HBV. High risk heterosexual activity was identified as the major risk factor for HBV acquisition, responsible for 21 cases (58.3%). In seven cases (22.2%), an iatrogenic mode of infection was suggested. Although HBV genotyping was not performed, in two of these seven cases there was a strong evidence of a true iatrogenic infection (history of blood transfusion before infection, and an accidental needlestick injury from a known HBV carrier). In the case of the accidental needlestick injury in a public healthcare worker, despite a prophylactic HBV vaccination, protective levels of anti HBs antibodies were not developed. In five additional patients, iatrogenic HBV acquisition was highly likely, with inpatient hospital procedures (for example, invasive dental

**Table 1** Patients' clinical characteristics

| Patient number | Sex | Age | Year of disease acquisition | Route of infection | Maximal ALT (× UNL) | Previous HBV vaccine | Chronicity |
|---|---|---|---|---|---|---|---|
| 1 | Male | 28 | 2002 | Occupational | 80 | No | No |
| 2 | Male | 29 | 2002 | Sexual contact | 35 | No | No |
| 3 | Male | 26 | 2002 | Sexual contact | 70 | No | No |
| 4 | Female | 23 | 2002 | Iatrogenic | 90 | No | No |
| 5 | Male | 59 | 2002 | Sexual contact | 17 | No | No |
| 6 | Male | 30 | 2002 | Sexual contact | 50 | No | No |
| 7 | Male | 68 | 2002 | Household contact | 38 | Yes | No |
| 8 | Female | 44 | 2002 | Iatrogenic | 40 | No | No |
| 9 | Male | 29 | 2002 | Sexual contact | 48 | No | No |
| 10 | Male | 75 | 2002 | Iatrogenic | 15 | No | Yes |
| 11 | Male | 23 | 2002 | Sexual contact | 42 | No | No |
| 12 | Male | 36 | 2002 | Sexual contact | 51 | No | No |
| 13 | Male | 27 | 2002 | Iatrogenic | 38 | No | No |
| 14 | Male | 57 | 2002 | Iatrogenic | 19 | Yes | No |
| 15 | Male | 27 | 2002 | Sexual contact | 51 | No | No |
| 16 | Female | 21 | 2002 | IDUs | 90 | No | No |
| 17 | Male | 51 | 2002 | Undefined | 55 | No | No |
| 18 | Male | 39 | 2003 | Iatrogenic | 25 | No | No |
| 19 | Male | 30 | 2003 | Sexual contact | 66 | No | Yes |
| 20 | Male | 40 | 2003 | Sexual contact | 26 | No | No |
| 21 | Male | 54 | 2003 | Sexual contact | 98 | No | No |
| 22 | Female | 17 | 2003 | Sexual contact | 187 | No | No |
| 23 | Male | 43 | 2003 | Sexual contact | 33 | No | No |
| 24 | Female | 35 | 2003 | Iatrogenic | 36 | No | No |
| 25 | Male | 44 | 2003 | IDUs | 48 | No | Yes |
| 26 | Male | 41 | 2003 | Sexual contact | 55 | No | No |
| 27 | Male | 33 | 2003 | Undefined | 69 | No | No |
| 28 | Male | 27 | 2003 | Sexual contact | 54 | No | No |
| 29 | Male | 70 | 2003 | Undefined | 59 | No | No |
| 30 | Male | 33 | 2003 | Sexual contact | 32 | No | No |
| 31 | Male | 47 | 2003 | Sexual contact | 51 | No | No |
| 32 | Male | 27 | 2003 | Sexual contact | 51 | No | No |
| 33 | Female | 25 | 2003 | Sexual contact | 71 | No | No |
| 34 | Male | 31 | 2003 | Sexual contact | 65 | No | No |
| 35 | Male | 44 | 2003 | Undefined | 77 | No | No |
| 36 | Female | 29 | 2003 | Sexual contact | 88 | No | No |

UNL, upper limit of normal; IDUs, injection drug users.

treatment, surgery, repeated electromyography tests including the use of needles), performed weeks to months before symptomatic presentation. A detailed questionnaire ruled out other possible modes of infection. Cases of HBV acquisition presumed iatrogenic were completely independent, and followed treatment in several medical centres in central Israel.

A single case of exposure to an HBV carrier household member was reported despite prophylactic vaccination (three injections in a six month period); one patient was probably infected through a non-medical occupational exposure; two cases involved injected drugs, and four cases remained undefined despite a thorough investigation. Table 2 shows the main modes of viral transmission as distributed by the patient's age.

**Table 2** Routes of infection distributed by the patients' age

| Patient's age | Sexual contact | Iatrogenic | Other | Total |
|---|---|---|---|---|
| 16–29 | 10 | 2 | 2 | 14 |
| 30–39 | 5 | 2 | 1 | 8 |
| 40–49 | 4 | 1 | 2 | 7 |
| 50–59 | 2 | 1 | 1 | 4 |
| 60–69 | – | – | 1 | 1 |
| 70–79 | – | 1 | 1 | 2 |

## DISCUSSION

A noticeable decline in the incidence of acute HBV infection has been reported since the introduction of vaccination policy worldwide.[1 7–10] In the year 2000 routine HBV vaccination was implemented in 116 countries.[11] Reports from countries who adopted this vaccination programme show as much as 70% decline in acute HBV cases.[1 7–9] Our study is the first to describe the incidence of acute HBV infection in Israel since the introduction of vaccination policy in this country in the mid-1990s. According to the Israeli Ministry of Health recommendations, candidates for the vaccination programme in Israel are infants and children, household contacts of HBV carriers, healthcare workers, haemodialysis patients, patients requiring repeat blood transfusions, and injection drug users. In contrast with the US policy, the formal vaccination policy in Israel does not include heterosexuals with a high risk of viral acquisition. While the definition of high risk heterosexual behaviour regarding viral acquisition is arbitrary, descriptions in the literature include multiple sexual partners (especially in a short period of time), or a repeated pattern of unprotected intercourse.[1]

The liver unit at the Tel-Aviv Sourasky Medical Center, a tertiary referral centre, is one of several such units located in the coastal plain area of Israel. The data presented in our study, and particularly the number of cases of acute HBV during the two subsequent years reported here, seem surprisingly high given both the regional nature of our centre (taking into consideration that our liver unit is one of several liver units located in the centre of Israel), and the incidence of disease as published by district government offices. In fact, the review of laboratory data of HBc IgM in the past five years at our centre validates our finding, with a mean of 17 new cases of acute HBV infection annually. National statistics based on the official report of the Israeli Ministry of Health reports of a mean of 99.8 new cases of acute HBV infection yearly in Israel during the years 1999–2003 (http://www.health.gov.il/english/). Local statistics of the Tel-Aviv District Office of the Israeli Ministry of Health has registered 10–12 new cases of acute HBV infection within their jurisdiction in each year in the years 1999–2003. It seems that the local incidence of 2.25 per 100 000 adults, estimated in our study, is greater than official statistics, yet presumably underestimates the true local incidence of disease, considering cases treated at other liver units in Israel. Interestingly, in the current series, most (85.7%) of those affected by displaying high risk sexual behaviour were men. Despite the relative small absolute number of patients seen, both the overall disease incidences, and the role of high risk heterosexual activity as a predominant route of transmission, demand the attention of public health authorities. Although selection bias is a concern, our data point to a trend in HBV acquisition and represent somehow the centre of Israel. Further analysis of these data, and data from other centres, will help define more accurately specific populations in need of prophylactic vaccination. From a general public health point of view, catch up vaccination of non-vaccinated young adults might be the most useful approach.

Opposing trends regarding male homosexuality as a risk factor for viral acquisition have been reported in the past two decades. The decline in acute HBV cases in homosexual men was initially believed to be linked to public education regarding safe sexual practices.[12 13] However, subsequent studies have suggested that the decline was merely temporary, with an eventual return to high risk sexual practices.[14] In the Netherlands, although homosexual contact is one of the more common causes of HBV transmission, there is little spread of the virus from the homosexual to the heterosexual population.[15] Of the 36 patients reported in our cohort, a single case of acute HBV infection was acquired through homosexual activity.

Transmission of HBV via transfusion of blood and plasma derived products has been eliminated in most countries through donor screening for HBsAg, and by viral inactivation procedures.[16] Of the two patients in this study who acquired the virus through an iatrogenic route, one was transfusion related. It is a common practice in blood banks in Israel to test blood donor candidates for HBsAg, but anti-HBc IgM antibodies were not routinely included as part of the screening profile until recently. The ''window'' period, during which only HBc IgM antibodies may be positive, is an important issue that calls for further attention in blood donor selection. Williams *et al*[17] have estimated that 0.4% of blood donors admit to high risk behaviour within the three months before blood donation, supporting the possibility of HBV contamination from donors in the incubation period.

In our cohort, five additional patients had a high probability of an iatrogenically acquired HBV because of a suggestive history, and after exclusion of all other possible modes of viral transmission. These patients probably acquired HBV through contaminated medical instruments such as electromyography needles and dental instruments. Hepatitis B infection in the healthcare setting is a known and reported hazard. Gerberding[18] found that hepatitis B is the most commonly transmitted blood borne virus in the healthcare setting. Residents of nursing homes, especially those who need repeated injections or blood testing, are particularly exposed to blood borne viruses.[19] However, despite a recent report of transmission of blood borne viral infection from surgeon to patients in both high risk and low risk surgical procedures, the transmission of blood borne viruses from healthcare workers to patients is uncommon.[20 21] The comparatively high incidence of iatrogenic infection that we have found (19.4%) warrants special attention. To minimise iatrogenic transmission, we recommend the completion of a thorough questionnaire before blood donation, and routine donor candidate testing for HBc IgM and IgG antibodies. Including HBc IgM serology in blood donor screening

programme might assist with the detection of those blood donor candidates who appeared to be infected with HBV and seem to be at the ''window phase'', in which the routine screening testing for HBsAg might be negative. Additionally, we suggest rigid enforcement of instrument sterilisation in all clinics where medical procedures are performed. While the periodic testing of all medical personnel for HBsAg might largely avoid health care personnel to patient transmission, this would be impractical and is thus best reserved for personnel who in routine screening tests have abnormal liver function. Testing for HBsAg titre will ensure healthcare personnel protection.

Injection drug users are an extremely high risk group for acquisition of blood borne viruses. In general, the decline in the incidence of acute HBV infection in injection drug users has been seen during the past decade.[1 22] Syringe and needle exchange are taking place, and drug addiction clinics offer hepatitis B vaccination. However, despite this decline, continual transmission of HBV among people who are injection drug users has been reported.[9 23–25] Two interesting reports from countries with a low HBV infection prevalence emphasise the relation between drug injection and rates of hepatitis B infection. In Finland[26] a threefold increase in acute HBV infection incidence seen over a three year period reflected the growing number of injection drug users in that country. A Swedish study[27] found injection drug use as the probable route of transmission in 46% of the patients infected. Furthermore, Hagan *et al*[28] suggested that under-reporting of acute hepatitis B and C in injection drug users raises questions regarding the true incidence of disease in this particular population.

Progression to chronic hepatitis B generally occurs in less than 10% of healthy adults.[2 29] In our series, three patients (8.33%) progressed to a chronic state. One of these patients was an elderly man with chronic diseases and frequent treatments with immune suppressant drugs. In the two additional cases of progression to chronic hepatitis B infection, no obvious risk factors for chronicity were identified, thus emphasising the importance of HBV infection prevention.

In conclusion, this study emphasises the importance of a thorough HBV surveillance programme to define high risk groups for disease acquisition. We presented 36 new cases of acute HBV infection seen in our liver unit during a two year study period. Men, aged 20–60 years, with a history of high risk heterosexual activity, were the most significant group at risk for acquiring HBV. Given these findings, it seems that Israel's current vaccination policy is not sufficient to eliminate disease transmission. The expansion of recommendations to include more groups at risk, particularly sexually active heterosexuals with high risk behaviour, deserves consideration.


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